REMARKS

Reconsideration and withdrawal of the claim rejections are requested in view of the remarks herein. Examiner Lucas, SPE Housel and Practice Specialist Caputa are thanked for courtesies extended during the April 14, 2004 interview.

I. THE DOUBLE-PATENTING REJECTION IS ADDRESSED

Claims 12-15 and 18 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 84-91, 93-95, 141-143, 149 and 150 of U.S.S.N. 09/760,574. The issue of whether there is double patenting is contingent upon whether the claims of the pending applications are allowed, and in what form. For example, claims 141-143, 149 and 150 of U.S.S.N. 09/760,574 have been withdrawn from consideration, and may be cancelled and pursued in a separate application. Applicants believe that this application is in condition for allowance. Accordingly, it is requested that the provisional double-patenting rejection be withdrawn in this application and issued in U.S.S.N. 09/760,574, as is proscribed by MPEP §804(I)B.

II. THE REJECTION UNDER 35 U.S.C. §103 IS OVERCOME

Claims 12-15 and 18 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Klippmark *et al.* in view of Suzu *et al.* and in further view of Felgner *et al.* and Crowe *et al.* These references were also considered in light of the teachings of Wathen *et al.* and Babiuk *et al.* The rejection is traversed.

The instant invention relates to an immunogenic composition or vaccine against BPIV-3 comprising a DNA plasmid that expresses BPIV-3 HN protein, F protein or both HN and F proteins. As was demonstrated by the data presented in the Declaration by Dr. Jean-Christophe Audonnet under 37 C.F.R. §1.132, filed on November 3, 2003, the claimed compositions are efficacious as vaccines in bovine animals. The fact that the plasmid DNA compositions of the invention can act as vaccines and confer protection is surprising and unexpected.

As discussed in the Amendment filed on November 3, 2003, and in the interview of April 14, 2004, Klippmark does not teach a plasmid vaccine against BPIV-3; and merely cites other studies:

> Several studies have shown that animals may be protected with whole virus and subunit vaccines containing both human and bovine PIV3 components (Morein *et al.*, 1983; Ray *et al.*, 1985). The two surface glycoproteins HN and F are important for the establishment of protection against disease (Morein *et al.*, 1983;

> Spriggs *et al.*, 1987). A mixture of both surface glycoproteins, HN and F (Ray *et al.*, 1988*a*), can induce protection against PIV3, as do HN and F proteins expressed by vaccinia virus and baculovirus recombinants (Spriggs *et al.*, 1987; van Wyke Coelingh *et al.*, 1987 [sic]).

The Morein reference shows that HN and F proteins, administered as multimeric micelles, elicited an immune response in mice, but not in lambs unless an adjuvant was added to the preparation. On page 1567, the authors state that they do not know why the adjuvant was necessary in lambs, but hypothesize that "it may be due to species differences". Therefore, they were clearly unable to extrapolate their results from rodents to ruminants. They also state, on the same page, that "the problem of efficient presentation of the antigen remains". So, not only are recombinant DNA vaccines not taught or suggested in Morein, the authors were unable to demonstrate ideal, or even consistent results using subunit vaccines.

The Examiner states, on page 6 of the Office Action, that the Applicants have misapplied Morein by ignoring the fact that Morein teaches the use of an adjuvant. Applicants would argue that the Examiner has misapplied Morein by dismissing the fact that it actually teaches away from the instant invention. As is admitted on page 6 of the Office Action, "Morein indicates that a composition comprising only the HN and F proteins (or plasmids encoding them) may not be effective vaccines in ruminants". The fact that they solve the problem by adding an adjuvant has no bearing on the fact that the inventors of the instant application have demonstrated efficacy, in direct contradiction to the teachings of Morein, without the use of an adjuvant. While the current claim language is open and includes the possibility that an adjuvant may be included, the point is that an adjuvant is not required, as was the case in Morein. Furthermore, given the unpredictability in the art relating to DNA administration and expression, and to correct folding and antigenicity of the resulting protein, teachings of vaccination with a protein cannot be extrapolated to teachings of vaccination with a DNA plasmid.

Ray showed an immune response in hamsters immunized with a combination of HN and F proteins, but not with inactivated whole virus that also contains HN and F proteins. As was true with Morein, predictable results were not obtained in hamsters by Ray. Given the potential interspecies variability demonstrated by Morein, there is no reason to think that either the teachings of Morein or Ray could be extended to bovine animals.

Spriggs *et al.* deals with the inoculation of cotton rats with recombinant HN and/or F proteins, prepared from cells infected with vaccinia virus. Vaccinia virus was used in this study

simply as a mechanism to produce recombinant proteins. In the last sentence of Spriggs, the authors state that their study could be a useful foundation for further investigations, such as "for testing the general usefulness of live recombinant viruses as vaccines". So not only does Spriggs not teach how to use a recombinant virus as a vaccine, it states that the feasibility of doing so was in doubt. Furthermore, there is no teaching or even suggestion in Spriggs that a DNA plasmid vaccine would be effective in an immunogenic composition or vaccine against BIV-3. Similarly, van Wyke Coelingh *et al.* showed an immune response in cotton rats inoculated with recombinant HN protein produced in baculoviral vectors. In addition to not teaching or suggesting the instant invention, as discussed above, the efficacy of the same composition may vary between rodents and bovines.

In view of the above, it is submitted that Klippmark does not teach "that the BPIV-3 HN and F proteins are able to induce protective responses in animals", as is stated on page 5 of the Office Action. At best, Klippmark only refers to studies that relate to the use of PIV-3 HN and F proteins in vaccines that were tested on rodents. The references cited by Klippmark, particularly Morein *et al.*, provide no expectation of success in larger animals. Further, these references cannot be extrapolated to the instant invention because there is no indication that the results achieved by administration of a protein-based vaccine correlate with those of administration of a DNA plasmid-based vaccine.

In further support of the Applicants' position, enclosed is a review article by Schultz *et al.* dealing with DNA vaccines (copy enclosed). The first section on page 203, entitled "Effect of Antiviral DNA Vaccines in Larger Species", states that "[s]everal DNA vaccines have proven efficacious in small animal models, especially mouse models", but that "[i]n larger species, DNA vaccines were less effective". Schultz *et al.* go on to discuss specific problems that are faced in larger animals, and some of the strategies investigators have used to improve the efficiency of DNA vaccines in larger animals. Therefore, it is clear from the teachings of Schultz *et al.* that results of vaccine studies cannot be extrapolated from one species to another, particularly from a small animal, such as a rodent, to a larger animal, such as a bovine.

While Suzu *et al.* supplies the RNA and deduced amino acid sequences of BPIV-3 HN and F proteins, it does not remedy any of the deficiencies of Klippmark.

Further, Felgner provides broad suggestions regarding the potential use of DNA plasmids as vaccines; however, Felgner does not teach plasmids encoding BPIV-3 proteins. In addition,

the only *in vivo* data relating to viral antigens provided by Felgner deals with HIV proteins expressed in mice. As discussed above, results obtained in mice cannot be extrapolated to larger animals, particularly in the complicated area of immune response. Also, Felgner does not teach or suggest the use of plasmids in eliciting an immune response against BPIV-3, which is of a completely different genera, family and order than HIV. (BPIV-3 is a paramyxovirus, whereas HIV is a lentivirus.) There is no indication, teaching or suggestion that any of the experiments in Felgner can be applied to the instant invention.

Crowe provides a non-enabling report of studies conducted by other parties. The section dealing with DNA immunization teaches away for the instant invention by suggesting that vaccination with plasmids expressing influenza A virus proteins "might prove useful in immunization strategies for RSV and PIV3" (p. 419). No plasmid construction or result of vaccination of bovines against BPIV-3 is described in this document.

It is also taught by Schultz *et al.*, in the abstract, that the antigen used bears on the efficacy of a vaccine. "The success of DNA immunization depends on a variety of parameters (e.g. type of antigen, method of application and usage of adjuvants)." Therefore, Schultz *et al.* supports Applicants' argument that DNA vaccine data cannot be extrapolated from one antigen to another. Rather, a protective effect must be demonstrated in a particular animal species using a particular antigen, as has been done in this case.

Babiuk *et al.* relates to herpesvirus-1, and is not relevant. Wathen also teaches away from the instant invention, as it advocates the use of a glycoprotein that is a chimera between HN and F to improve a vaccine.

The Examiner is respectfully reminded that "obvious to try" is not the standard for formulating a *prima facie* case of obviousness under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). Also, the Examiner is additionally respectfully reminded that for the Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

In this case, the Office Action relies on the combination of six different references, some of which do not teach anything at all, but rather, report results obtained by other researchers. Although it may have been obvious to try a DNA plasmid vaccine against BPIV-3, given the variability between viruses and the incongruous results obtained from one animal species to the

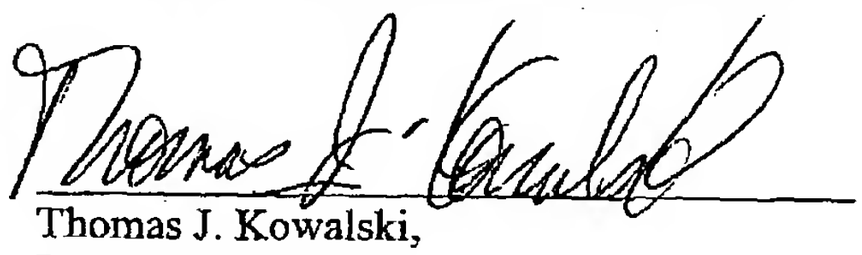
next, there has been no demonstration by the Examiner that the skilled artisan could reasonably have expected success in bovines using an immunogenic composition or vaccine containing a plasmid with DNA encoding BPIV-3 HN and/or F proteins. The fact that the inventors of the instant application have been able to demonstrate efficacy is surprising and unexpected.

Although the cited references have been dealt with somewhat individually above, the failings of the cited references to predict, teach or suggest the success of the claimed invention are not remedied by combination with one another. Furthermore, the art cited by the Examiner and presented by the Applicants supports the argument that teachings in the vaccine field cannot be extrapolated from small animals to large animals, from one antigen to another, or from a protein vaccine to a DNA vaccine. It is therefore submitted that the claimed invention is not obvious over the cited references. Therefore, reconsideration and withdrawal of the 35 U.S.C. §103 rejection are respectfully requested.

CONCLUSION

Applicants believe that the application is in condition for allowance, and favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. Alternatively, consideration and entry of this paper are requested, as it places this application into better condition for purposes of appeal.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

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